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Granulocyte-macrophage colony stimulating factor in COVID-19: friend or foe?

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See Articles page e410

A biphasic model of COVID-19 is now well-established, with an initial viraemic phase, followed by a host hyperinflammatory phase in a subgroup of patients with an inappropriate, excessive immune response associated with high mortality, which might respond to immunomodulatory therapy.[1] Randomised controlled trials (eg, RECOVERY and REMAP-CAP) have shown the efficacy of corticosteroids[2] and interleukin (IL)-6 blockade in reducing mortality in patients with severe COVID-19, although there have been mixed results with IL-6 inhibition.[3]

Granulocyte-macrophage colony stimulating factor (GM-CSF) is an immunoregulatory cytokine that exemplifies the complexity and challenges of drug trials in COVID-19, given its role in both the pro-inflammatory hypercytokinaemia leading to monocyte and macrophage activation, and in antiviral immunity. There is rationale for both therapeutic blockade and recombinant administration of GM-CSF,[4,5] and there is accumulating evidence for targeting GM-CSF in patients with severe COVID-19. Bronchoalveolar lavage fluid analysis from patients with severe COVID-19 has shown clonally expanded tissue-resident memory-like Th17 cells with a potentially pathogenic profile of cytokine expression of GM-CSF and IL-17A; these memory-like Th17 cells are thought to interact with lung macrophages and cytotoxic $CD8^+$ T cells, and are associated with disease severity and lung damage.[6] High GM-CSF protein concentrations in the serum of patients with COVID-19 is associated with a more severe clinical course.[6] Additionally, inhibiting GM-CSF might have advantages over targeting IL-6 with respect to safety, because there might be less pronounced pharmacodynamic suppression of C-reactive protein and fever, which can facilitate the detection of secondary infection. Cohort studies have shown an efficacy signal for drugs targeting GM-CSF (lenzilumab)[7] or its receptor (mavrilimumab),[8] but robust controlled trial data have been eagerly anticipated.

In *The Lancet Rheumatology*, Paul Cremer and colleagues[9] report the results of their double-blind, randomised trial of mavrilimumab in patients with severe COVID-19 pneumonia and systemic hyperinflammation (MASH-COVID). The study did not meet the primary endpoint (ie, proportion of patients free of supplemental oxygen support at day 14), which might be due to several factors, the smaller-than-planned sample size being probably the most important. Due to the slow recruitment rate, the study was terminated after enrolment of 20 patients per treatment group, instead of the 30 per group estimated to be needed based on preliminary case-control data. The study design has a badge of rigour that accompanies a double-blind, placebo-controlled trial (which is challenging in the COVID-19 pandemic). However, although the intended population was patients with severe COVID-19 pneumonia with hyperinflammation, enrolled patients probably had mild to moderate COVID-19 pneumonia with hypoxaemia (receipt of invasive mechanical ventilation was excluded) and a threshold C-reactive protein concentration of more than 5 mg/dL (ie, 50 mg/L), which might be set too low to identify a subgroup of patients with hyperinflammation.

The efficacy of mavrilimumab might have also been masked by the heterogeneity of concomitant, permitted medications. Before random assignment, 26 (65%) of 40 patients were treated with corticosteroids and 30 (75%) patients were treated with remdesivir.[9] After random assignment, an additional five patients were started on corticosteroids, ten patients received convalescent plasma, three patients received remdesivir, and two patients received tocilizumab.[9] Although it seems that these additional medications had no significant influence on the primary and secondary outcomes, the actual contribution of all concomitant (especially when combined) and previous therapies is difficult to unpick and might confer potential confounding. Furthermore, patients were enrolled between May and September, 2020 (after the first COVID-19 surge), and standard of care definitions changed over time by virtue of the accrual of clinical experience, improved supportive care, and advances in background therapies. The changing standard of care in the placebo group could partially explain the finding that more patients than expected in this group were no longer in receipt of supplemental oxygen by day 14, and consequently the risk reduction with

mavrilimumab was lower than predicted. Despite the negative primary outcome, patients who received mavrilimumab were numerically more likely to be alive and without respiratory failure by day 28, consistent at day 60 of follow-up, which might be more relevant clinical endpoints. Reassuringly, the adverse event rate was similar between the groups.

The potential benefits of targeting GM-CSF in the context of a virally driven illness need to be carefully balanced with the potential risk associated with blocking the role of this cytokine in tissue homoeostasis, including maintenance of alveolar capillary barrier integrity, host defence (antiviral immunity), and epithelial repair. In February, 2021, there were two press releases describing two opposing therapeutic approaches in COVID-19. One was a phase 2 trial (OSCAR) of the anti-GM-CSF antibody otilimab, which did not meet the primary endpoint but supported the approach of blocking GM-CSF in a prespecified subgroup analysis of patients older than 70 years. The second was a clinical trial administering inhaled or intravenous recombinant GM-CSF (sargramostim), which did meet the primary endpoint of improvement oxygenation levels. The full publications of these trial findings following peer-review are awaited, and we agree with Cremer and colleagues that the results of the current study support further investigation in larger randomised controlled trials.[9] It is likely that, analogous to other cytokine inhibitors,[10] the value of therapies targeting (or perhaps even supplementing) the GM-CSF axis is likely to depend on patient selection and timing of intervention in the disease course.

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*Puja Mehta, Rachel C Chambers, *Lorenzo Dagna*
dagna.lorenzo@unisr.it

Centre for Inflammation and Tissue Repair, Division of Medicine, University College London, London, UK (PM, RCC); Department of Rheumatology, University College London Hospital NHS Trust, London, UK (PM); Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS San Raffaele Scientific Institute, Milan 20132, Italy (LD); Vita-Salute San Raffaele University, Milan, Italy (LD)

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For the **otilimab press release** see https://www.gsk.com/en-gb/media/press-releases/gsk-announces-otilimab-data-for-treatment-of-covid-19

For the **sargramostim press release** see https://www.prnewswire.com/news-releases/sarpac-clinical-trial-of-leukine-sargramostim-rhu-gm-csf-in-hospitalized-covid-19-patients-meets-primary-endpoint-of-significant-improvement-in-lung-function-301236275.html

Managing patients with rheumatic diseases treated with rituximab during the COVID-19 pandemic

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See **Articles** page e419

From the start of the COVID-19 pandemic, patients treated with rituximab approached their rheumatology team in large numbers to ask their opinion on the risk of COVID-19, and whether they should continue with rituximab treatment or not. Later in the pandemic, the relevance of vaccination against COVID-19 also became a concern.

Preliminary answers to these questions appeared in a fragmented way as initial reports of isolated observations in patients receiving rituximab emerged.[1] Very rapid establishment of registries to examine COVID-19 outcomes in patients with rheumatic and musculoskeletal diseases, such as the COVID-19 Global Rheumatology Alliance[2] and the French RMD COVID-19